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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/090,516	Applicant(s) YU ET AL.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) 7 and 8 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-8 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence alignments* .

DETAILED ACTION

Application Status

[1] Claims 1-8 are pending in the application.

[2] During a telephone conversation with David W. Hibler on May 5, 2003, the examiner inquired as to the relationship of SEQ ID NO:1 to SEQ ID NO:3 and the relationship of SEQ ID NO:2 to SEQ ID NO:4. Mr. Hibler indicated that SEQ ID NO:3 is a fragment of SEQ ID NO:1 and SEQ ID NO:4 is a fragment of SEQ ID NO:2.

[3] Also, during the same telephone conversation on May 5, 2003, Mr. Hibler indicated that claim 5 should depend from claim 4 instead of depending from itself.

Election/Restrictions

[4] Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim(s) 1-6, drawn to an isolated nucleic acid encoding SEQ ID NO:2 including SEQ ID NO:1 and an isolated nucleic acid encoding SEQ ID NO:4 including SEQ ID NO:3, classified in class 536, subclass 23.5.

II. Claim(s) 7 and 8, drawn to a substantially isolated protein of SEQ ID NO:2 and variants thereof, classified in class 530, subclass 350.

[5] The inventions are distinct, each from the other because:

[6] The nucleic acid of Group I and the polypeptide of Group II each comprises a chemically unrelated structure capable of separate manufacture, use and effect. The nucleic acid of Group I has other utility besides encoding polypeptides such as being used as a hybridization probe and the polypeptide of Group II can be made by another method such as purification from the natural source or chemical synthesis.

[7] MPEP § 803 sets forth two criteria for restricting between patentably distinct inventions – 1) the inventions must be independent or distinct and 2) there must be a serious burden on the examiner. MPEP § 803 states, "For purposes of the initial requirement, a serious burden on the examiner may be *prima*

facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02". Because the inventions of Groups I and II are distinct for the reasons given above, have separate classification, and each of the inventions requires a separate patent and non-patent literature and sequence search, restriction for examination purposes is proper.

[8] During a telephone conversation with Mr. David W. Hibler on May 5, 2003 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-6.

[9] Affirmation of this election must be made by applicant in replying to this Office action.

[10] Claims 7 and 8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

[11] Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

[12] Receipt of an Information Disclosure Statement filed as Paper No. 5 is acknowledged. The references cited on Form PTO-1449 have been considered by the examiner and a signed and dated copy of Form PTO-1449 is attached to the instant Office action.

Priority

[13] The examiner acknowledges applicant's claim for domestic priority under 35 USC § 119(e) to earlier filed provisional application number 60/275,011, filed March 12, 2001. It is noted that the sequences of SEQ ID NO:1-4 of the instant application are disclosed in provisional application number 60/275,011.

Claim Objection(s)

[14] Applicant is advised that should claim 2 be found allowable, claim 3 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

[15] Claim 5 is objected to under 37 CFR 1.75(c) as being an improper dependent claim as the claim is dependent upon itself. In view of the aforementioned telephone conversation (see item 3 above) and in the interest of advancing prosecution, claim 5 has been examined as though the claim depends from claim 4. It is suggested that applicant amend claim 5 to depend from claim 4.

[16] Applicant is advised that should claim 5 be found allowable, claim 6 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

[17] Claim 5 is objected to because of the following informalities: the term "wherein nucleotide sequence" in line 2 is grammatically incorrect and should be replaced with, for example, "wherein said nucleotide sequence" or "wherein the nucleotide sequence". Appropriate correction is required.

Claim Rejection(s) - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[18] Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is confusing as SEQ ID NO:3 is not a subsequence of SEQ ID NO:1. It is noted that during a telephone conversation with Mr. Hibler (see item 2 above), it was indicated that SEQ ID NO:3 is an identical subsequence of SEQ ID NO:1. However, alignment of SEQ ID NO:3 and SEQ ID NO:1 indicates that there is a mismatch at position 4875. The Paper Copy of the sequence listing shows that SEQ ID NO:3 has A at position 4875 while SEQ ID NO:1 has G at this position. Based on the evidence provided in the Paper Copy of the sequence listing, SEQ ID NO:3 is not an identical subsequence of SEQ ID NO:1. In the interest of advancing prosecution, claim 2 has been examined as though the claim were an independent claim drawn to an isolated nucleic acid molecule comprising SEQ ID NO:1. It is noted that the presence of A at position 4875 of SEQ ID NO:3 introduces an in-frame stop codon at nucleotides 4873-4875 of SEQ ID NO:3.

Claim Rejection(s) - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[19] Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Claim 1 is drawn to an isolated nucleic acid comprising SEQ ID NO:3. Claims 2 and 3 are drawn to an isolated nucleic acid comprising SEQ ID NO:1. Claim 4 is drawn to an isolated nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:4. Claim 5 further limits the nucleic acid of claim 4 to encoding SEQ ID NO:2. Claim 6 is drawn to an isolated nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:2.

Regarding a specific utility for the claimed nucleic acids, applicant asserts various utilities for the claimed nucleic acids including protein expression, use as hybridization probes, antisense oligonucleotides, detection of mutations or polymorphisms for disease diagnosis, use as a therapeutic agent, and a drug target. The use of a nucleic acid for protein expression, hybridization, or antisense is

not specific as virtually *any* nucleic acid has utility for protein expression or for use as hybridization probes and antisense oligonucleotides. Furthermore, regarding the use of the claimed nucleic acid for the detection of mutation for disease diagnosis or for use as a therapeutic agent and drug target, it is noted that the specification fails to disclose a nexus between the claimed nucleic acid and a *specific* disease state that may be useful for identifying, diagnosing, or therapeutically treating a disease state or condition. Therefore, the asserted utilities are not specific to the claimed nucleic acids and are instead general utilities that would be applicable to the broad class of nucleic acids and/or would require further experimentation to identify or confirm a "real world" context of use. Thus, the claimed nucleic acids have no specific and substantial asserted utility.

Regarding a substantial utility for the claimed nucleic acids, applicant asserts the polypeptides of SEQ ID NO:2 and 4 encoded by the nucleic acids of SEQ ID NO:1 and 3, respectively, share sequence similarity with mammalian membrane proteins (page 1, lines 9-10 of the instant specification) and share structural similarity with mammalian proteins such as the murine TEN-M4/cdz protein and proteins identified as γ-heregulins (page 2, lines 5-11 of the instant specification). It is noted that applicant has presented no explicit assertion of the function of the polypeptides of SEQ ID NO:2 and 4. Even if applicant's statement that SEQ ID NO:2 and 4, encoded by the nucleic acids of SEQ ID NO:1 and 3, respectively, share sequence similarity with murine TEN-M4/cdz protein γ-heregulin is to be construed as an implied assertion of function – which it is not - further experimentation would be required to establish a real-world use for the polypeptides and encoding nucleic acids as explained in detail below. Regarding SEQ ID NO:2 and 4 as TEN-M4/cdz proteins, a sequence search reveals that SEQ ID NO:2 and 4 share the highest percentage identity with mouse Ten-m4, also called DOC4 (see attached sequence comparison). Wang et al. (*EMBO J* 17:3619-3630) and Oohashi et al. (*J Cell Biol* 145:563-577) describe cloning and characterization of mouse Ten-m4 (referred to as DOC4 by Wang et al. but later referred to as Ten-m4 by Oohashi et al. due to its homology to *Drosophila* Ten-m/Odz). Experiments by Wang et al. led them to speculate a stress-response function by Ten-m4 (page 3628, right column, bottom). Oohashi et al. later acknowledged that Ten-m4 expression is induced by cellular stress, however regarding a

stress response function of Ten-m4, Oohashi et al. state, "it is not clear which function is propagated by this protein" (page 576, last full paragraph). Oohashi et al. further state that additional experimentation is required to determine the function of Ten-m4 by stating, "To obtain direct evidence for possible roles of ten-m proteins during development and disease we have... ...generated mutant mice" and that "[t]he analysis of these mice will provide further insights into the function(s) of these interesting molecules" (page 576, right column, last full paragraph). Thus, from the teachings of Wang et al. and Oohashi et al., a skilled artisan would recognize that the function of Ten-m4 is undefined and further experimentation would be required to define such function.

Regarding SEQ ID NO:2 and 4 as γ-heregulin proteins, Wang et al. teach "[a] database search reveals that the 632 N-terminal amino acids of the human homolog of DOC4 (>90% identity) are found as part of a novel secreted protein referred to as γ-heregulin" (page 3626, right column, bottom). Schaefer et al. (*Oncogene* 15:1385-1394) who disclose the initial cloning and characterization of γ-heregulin, teach the 560 amino acid N-terminus of γ-heregulin is proposed to function as a signal sequence that mediates secretion across the cell membrane (page 1386, left column and page 1387, left column, middle). Schaefer et al. further teach that γ-heregulin is an autocrine growth factor for the breast tumor cell line MDA-MB-175. However, it is noted that a sequence search reveals that, while both SEQ ID NO:2 and 4 are 100% identical to amino acids 1-560 of human γ-heregulin, there is almost no similarity between the proteins past amino acid 560 (see attached sequence alignment). Overall, SEQ ID NO:2 and 4 are *only* 20.3% identical to human γ-heregulin. The state of the art indicates that functional assignment based on sequence similarity or identity alone, particularly in the instant case where the homologous sequences share a relatively low sequence identity, can lead to an erroneous functional assignment. As evidence of the state of the art, Brenner (*Trends Genet* 15 :132-133) teaches that it is impossible to determine the reliability of a functional assignment of a protein without verification by laboratory experiments (page 132, left column). Further evidence is provided by Scott et al. (*Nat Genet* 21:440-443) who teach an erroneous functional assignment of a protein based on 45% sequence identity to a human

sulfate transporter (page 440, left column, middle). Scott et al. teach "[w]e conclude that pendrin does not function as a sulfate transporter, as suggested by its close homology to other sulfate transporters, but instead functions as a sodium-independent transporter of chloride and iodide. These results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant sequence homology to proteins of known function" (page 441, left column, bottom). Therefore, based on the relatively low overall identity of SEQ ID NO:2 and 4 with human γ-heregulin, a skilled artisan would recognize that further research is required to confirm the function of the polypeptides of SEQ ID NO:2 and 4 as γ-heregulin autocrine growth factors.

Therefore, it is unclear as to how the polypeptides of SEQ ID NO:2 and 4 or encoding nucleic acids of SEQ ID NO:1 and 3 would be useful without further experimentation to identify a real-world use. In the instant case further experimentation is required in order to identify a "real world" context of use for the polynucleotides of SEQ ID NO:1 and 3. This type of utility is not considered a "substantial utility". See e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. Thus, the claimed nucleic acids are not supported by a substantial asserted utility. Here the claimed polynucleotide is suitable only for additional research.

For the reasons stated above, the claimed nucleic acids have no specific and substantial utility and the examiner can find no disclosure of a well-established utility for the claimed nucleic acids.

Claim Rejection(s) - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[20] Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial or specific asserted utility or a well established utility for the reasons set forth in item 18 above, one skilled in the art clearly would not know how to use the claimed invention.

[21] Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 4 is drawn to a genus of nucleic acids comprising a nucleotide sequence encoding SEQ ID NO:4. It is noted that SEQ ID NO:4 is an N-terminal fragment of the open reading frame of SEQ ID NO:2. However, the specification fails to disclose whether nucleic acids encoding SEQ ID NO:4 would cross an intron/exon splice junction. Without such disclosure, the genus of nucleic acids of claim 4 encompasses full-length genes that have not been described in the specification. A description of a genus of nucleic acids may be achieved by means of a recitation of a representative number of nucleic acids, defined by the nucleotide sequence, falling within the scope of the genus or of a recitation of a recitation of a structural feature common to all members of the genus, which members constitute substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed Cir. 1997). In the instant case, the specification discloses only a single common structural feature shared by members of the claimed genus, i.e., a nucleic acid encoding SEQ ID NO:4. Since the claimed genus encompasses genes yet to be discovered, the disclosed structural feature does not constitute a substantial portion of the claimed genus. Furthermore, there is substantial variability among the species of nucleic acids encompassed within the genus of the claims as a nucleic acid encoding SEQ ID NO:4 is only a fragment of any full length gene. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of the single representative species of SEQ ID NO:1 and 3 fails to represent the entire genus of claimed nucleic acids and is insufficient to put one of skill in the art in possession of the attributes and features of

all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

It is noted that claim 1, drawn to an isolated nucleic acid comprising SEQ ID NO:3 has not been rejected under 35 USC 112, first paragraph, for a lack of written description. SEQ ID NO:3 has a sequence corresponding to nucleotides 1-4874 of the open reading frame of SEQ ID NO:1 with a mismatch at position 4875 resulting in an in-frame stop codon in the nucleotide sequence of SEQ ID NO:3 (see item 17 part a above). Also, because SEQ ID NO:3 is identical to the first 4874 nucleotides of the open reading frame of SEQ ID NO:1, SEQ ID NO:3 has a start codon. Thus, SEQ ID NO:3 would be considered a complete open reading frame and none of the species encompassed by the genus of nucleic acids of claim 1 would read on a full-length gene because any variation within the genus of nucleic acids of claim 1 would arise due to the addition of elements that are not part of the inventor's particular contribution. In contrast, SEQ ID NO:4 is an N-terminal fragment of SEQ ID NO:2 and while a nucleic acid encoding SEQ ID NO:4 would have a start codon, this nucleic acid would not necessarily have a stop codon. Therefore, the species encompassed within the genus of nucleic acids of claim 4 would read on other undisclosed nucleic acids including full-length genes and nucleic acids encoding a variety of proteins other than SEQ ID NO:4.

Conclusion

[22] The status of the claims is as follows:

- Claims 1-8 are pending.
- Claims 7 and 8 are withdrawn from consideration.
- Claims 1-6 are rejected.

[23] No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for official papers filed to Group 1600 is (703) 308-4242. Draft or informal FAX

communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

06/09/03